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=> s ((somatostatin analog?) or octreotide or somatostatin or octreotate)
L1       86875 ((SOMATOSTATIN ANALOG?) OR OCTREOTIDE OR SOMATOSTATIN OR OCTREOT
               ATE)

=> s oligonucl? or antisense
L2      226887 OLIGONUCL? OR ANTISENSE

=> s l1 and l2
L3         771 L1 AND L2

=> s l3 and conjugat? or link?
L4     1219308 L3 AND CONJUGAT? OR LINK?

=> s l3 and (conjugat? or link?)
L5          56 L3 AND (CONJUGAT? OR LINK?)

=> s l1 (5n) (conjugat? or link?) (5n) (oligonucl? or antisense)
L6           2 L1 (5N) (CONJUGAT? OR LINK?) (5N) (OLIGONUCL? OR ANTISENSE)

=> dup rem l6
PROCESSING COMPLETED FOR L6
L7           2 DUP REM L6 (0 DUPLICATES REMOVED)

=> d l7 1-2 ibib abs

L7   ANSWER 1 OF 2  CA  COPYRIGHT 2002 ACS
ACCESSION NUMBER:        135:190390  CA
TITLE:                   Antisense oligonucleotide
                         conjugates with somatostatin
                         analogs for treatment of tumors associated
                         with high leves of the somatostatin receptor
INVENTOR(S):             Eisenhut, Michael; Mier, Walter; Eritia, Ramon;
                         Haberkorn, Uwe
PATENT ASSIGNEE(S):      Deutsches Krebsforschungszentrum Stiftung des
                         Oeffentlichen Rechts, Germany
SOURCE:                  Ger. Offen., 16 pp.
                         CODEN: GWXXBX
DOCUMENT TYPE:           Patent
LANGUAGE:                German
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
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     DE 10006572       A1   20010823       DE 2000-10006572 20000214
     EP 1129725        A2   20010905       EP 2001-103466   20010214
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
     US 2001029035     A1   20011011       US 2001-781980   20010214
PRIORITY APPLN. INFO.:                    DE 2000-10006572 A  20000214
AB   The present invention concerns an oligonucleotide conjugate between an
     antisense DNA to an essential gene and a somatostatin analog.  The present
     invention concerns also this oligonucleotide conjugate contg. drug,
     preferably to the therapy of tumors, with which the somatostatin receptor
     (SSTR) is over-expressed.  The antisense DNA, which may contain base
     analogs or a modified backbone, is preferably directed against the bcl-2
     oncogene.  Prepn. of octreotide analogs of somatostatin
     and their conjugation with antisense
     oligonucleotides is demonstrated.

L7   ANSWER 2 OF 2  BIOSIS  COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER:   2001:300098  BIOSIS
DOCUMENT NUMBER:    PREV200100300098
TITLE:              Tumor-targeting peptide-oligonucleotide conjugates.
AUTHOR(S):          Mier, W. (1); Eritja, R. (1); Mohammed, A. (1); Haberkorn,
                    U. (1); Eisenhut, M. (1)
CORPORATE SOURCE:   (1) Nuclear Medicine, Universitaetsklinikum Heidelberg,
                    Heidelberg Germany
SOURCE:             Journal of Cancer Research and Clinical Oncology, (2001)
                    Vol. 127, No. Supplement 1, pp. S44. print.
                    Meeting Info.: Eleventh Congress of the Division of
                    Experimental Cancer Research of the German Cancer Society
                    Heidelberg, Germany April 04-06, 2001 German Cancer Society
                    . ISSN: 0171-5216.
DOCUMENT TYPE:      Conference
LANGUAGE:           English
SUMMARY LANGUAGE:   English


=> d his

     (FILE 'HOME' ENTERED AT 16:08:25 ON 31 JUL 2002)

     FILE 'BIOSIS, MEDLINE, SCISEARCH, CA' ENTERED AT 16:10:03 ON 31 JUL 2002
L1         86875 S ((SOMATOSTATIN ANALOG?) OR OCTREOTIDE OR SOMATOSTATIN OR OCTR
L2        226887 S OLIGONUCL? OR ANTISENSE
L3           771 S L1 AND L2
L4       1219308 S L3 AND CONJUGAT? OR LINK?
L5            56 S L3 AND (CONJUGAT? OR LINK?)
L6             2 S L1 (5N) (CONJUGAT? OR LINK?) (5N) (OLIGONUCL? OR ANTISENSE)
L7             2 DUP REM L6 (0 DUPLICATES REMOVED)

=> dup rem l5
PROCESSING COMPLETED FOR L5
L8            38 DUP REM L5 (18 DUPLICATES REMOVED)

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   3 FILES SEARCHED...
L9            27 L8 AND PY=<2000

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L9   ANSWER 1 OF 27  BIOSIS  COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER:   2001:65051  BIOSIS
DOCUMENT NUMBER:    PREV200100065051
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TITLE: Preparation and evaluation of tumor-targeting peptide-**oligonucleotide conjugates**.
AUTHOR(S): Mier, Walter (1); Eritja, Ramon; Mohammed, Ashour; Haberkorn, Uwe; Eisenhut, Michael
CORPORATE SOURCE: (1) Department of Nuclear Medicine, Universitaetsklinikum Heidelberg, INF 400, 69120, Heidelberg: walter_mier@med.uni-heidelberg.de Germany
SOURCE: Bioconjugate Chemistry, (**November December, 2000**) Vol. 11, No. 6, pp. 855-860. print.
ISSN: 1043-1802.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Enormous progress has been made in the development of **antisense** oligodeoxynucleotides (ODNs) as therapeutic agents inhibiting gene expression. Unfortunately, the therapeutical application of ODNs is still held back because of the low cellular uptake and the lack of specific transport into particular cells. In this paper, we report a drug-targeting system using **somatostatin** receptors (SSTRs) which are overexpressed in various tumors. Phosphorothioate ODNs were covalently **linked** to Tyr3-**octreotate**, an analogue of **somatostatin**. The peptide was assembled by solid-phase synthesis, oxidized to form the cyclic disulfide, and subsequently derivatized with a N-terminal maleimido functionality. 5'-Thiol derivatized phosphorothioate-ODNs directed against the protooncogene bcl-2 were **conjugated** to this maleimido-modified peptide. Binding studies revealed that the **conjugates** retain specific binding with nanomolar affinities to SSTRs (IC50-values between 1.83 and 2.52 nM). Furthermore, melting studies with complementary DNA revealed that the terminal **conjugation** of the ODNs did not significantly affect their hybridization affinity.

L9 ANSWER 2 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:61895 BIOSIS
DOCUMENT NUMBER: PREV200000061895
TITLE: Cloning of the mouse **somatostatin** receptor subtype 5 gene: Promoter structure and function.
AUTHOR(S): Gordon, David F. (1); Woodmansee, Whitney W.; Lewis, Suzanne R.; James, R. Andrew; Wood, William M.; Ridgway, E. Chester
CORPORATE SOURCE: (1) Division of Endocrinology, University of Colorado Health Sciences Center, 4200 East Ninth Avenue, Denver, CO USA
SOURCE: Endocrinology, (**Dec., 1999**) Vol. 140, No. 12, pp. 5598-5608.
ISSN: 0013-7227.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **Somatostatin** is a peptide hormone whose actions are mediated by five **somatostatin** receptor subtypes (sst1-5). In the pituitary, **somatostatin** inhibits TSH release from thyrotropes and GH release from somatotropes. We have shown that sst5 transcripts and protein are induced by thyroid hormone in TtT-97 thyrotropic tumors. To map sequences responsible for promoter activity in pituitary cells, we cloned the mouse sst5 coding region of 362 amino acids and 12 kb of upstream DNA. Initial transfection studies in TtT-97 or GH3 cells mapped high levels of basal promoter activity to a 5.6-kb fragment upstream of the translational start, whereas shorter genomic fragments had low activity. To identify the transcriptional start site we used 5' RACE with TtT-97 poly A+ RNA and a sst5 **antisense** coding region primer. Sequence comparison between the complementary DNA and the gene revealed that the mouse sst5 gene

contains 3 exons and 2 introns. The entire coding region was contained in exon 3. Two differently sized RACE products demonstrated alternate exon splicing of two untranslated exons in TtT-97 cells. A promoter fragment from -290/+48 **linked** to a luciferase reporter demonstrated 600- and 900-fold higher activity over a promoterless control in GH3 mammosomatotropes and TtT-97 thyrotropes, respectively, whereas a larger fragment extending to -6400 exhibited no additional promoter activity. Cloning of the sst5 gene will facilitate the mapping of basal and regulated responses at the transcriptional level.

L9 ANSWER 3 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:365535 BIOSIS
DOCUMENT NUMBER: PREV199699087891
TITLE: Transcriptional regulation of the junB promoter in mature B lymphocytes.
AUTHOR(S): Amato, Stephen F.; Nakajima, Koichi; Hirano, Toshio; Chiles, Thomas C. (1)
CORPORATE SOURCE: (1) Dep. Biol., Boston College, 411 Higgins Hall, Chestnut Hill, MA 02167 USA
SOURCE: Journal of Immunology, (1996) Vol. 157, No. 1, pp. 146-155. ISSN: 0022-1767.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The experiments presented herein were designed to understand the molecular mechanisms by which membrane Ig (mIg)dependent signals are integrated at the level of the junB promoter to induce gene transcription. Functional studies using chloramphenicol acetyltransferase reporter gene constructs that contained deleted 5' flanking region junB sequences identified a region located between -194 and -87 that contains an Ets binding site and a putative cAMP response element binding site (CRE-like). Point mutagenesis of the CRE-like site blocked junB promoter activation in response to mIg cross-**linking** in mature Bal17 B cells. Nuclear extract binding activity to a synthetic **oligonucleotide** containing the junB CRE-like site was detected in unstimulated B cells and was increased in response to mIg cross-**linking**. Binding activity was competed with unlabeled **oligonucleotides** that contained the junB CRE-like site or the **somatostatin** CRE consensus motif; the latter observation suggests that members of the activating transcription factor/CRE binding protein (CREB) family may mediate mIg-dependent junB transcription. Consistent with this interpretation, recombinant CREB and activating transcription factor proteins bound the junB CRE-like site, but did not interact with a mutant CRE-like site. Expression of a dominant negative CREB protein blocked mIg-mediated transcription from a junB CRE-like site-chloramphenicol acetyltransferase reporter gene. CRE-like nucleoprotein complexes from Bal17 B cells contained constitutively bound CREB-1, which was phosphorylated on serine 133 in response to mIg cross-**linking**. Activating transcription factor-1 protein was also constitutively expressed in CRE-like nucleoprotein complexes. Collectively, these results suggest that components of the protein kinase A signaling pathway are recruited by mIg to induce junB transcription.

L9 ANSWER 4 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:335931 BIOSIS
DOCUMENT NUMBER: PREV199699058287
TITLE: Estimation of the number of **somatostatin** neurons in the striatum: An in situ hybridization study using the optical fractionator method.
AUTHOR(S): West, Mark J. (1); Ostergaard, Karen; Andreassen, Ole A.; Finsen, Bente
CORPORATE SOURCE: (1) Dep. neurobiol., Inst. Anat., Univ. Aarhus, 8000 Aarhus Denmark
SOURCE: Journal of Comparative Neurology, (1996) Vol. 370, No. 1,

pp. 11-22.
ISSN: 0021-9967.
DOCUMENT TYPE: Article
LANGUAGE: English

AB **Somatostatin**-containing neurons of the striatum constitute fewer than 5% of the total neuronal population. Their involvement in the feedforward inhibition of the spiny projection neurons, the modulation of other interneurons, and the regulation of regional blood flow indicates that this small population of neurons plays an important role in the processing of information in the striatum. As a first step in developing a quantitative structural framework within which a more rigorous analysis can be made of the functional circuitry of the striatum, we used modern unbiased stereological techniques to make estimates of the total number of neurons expressing mRNA for **somatostatin** in the striatum of rats. The strategy developed involved the application of the optical fractionator technique to relatively thick tissue sections that were hybridized in situ with a relatively short **oligonucleotide** probe **conjugated** to a nonradioactive reporter molecule. The approach is generally applicable to other subpopulations of in situ hybridized cells in other parts of the brain and can provide a **link** between molecular neurobiology and stereology. The mean total number of neurons on one side of the striatum was estimated to be 21,300. An analysis of the sampling scheme indicated that counting no more than 200 neurons in a systematic sample of not more than 15 sections per individual results in an estimate with a precision that is more than sufficient for comparative and experimental studies. The issues that must be considered when analyzing in situ hybridized tissue with modern stereological methods, the interpretive caveats inherent in the resulting data, and the unique perspectives provided by data like that presented here for striatal **somatostatin** neurons are discussed.

L9 ANSWER 5 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:123334 BIOSIS
DOCUMENT NUMBER: PREV199698695469
TITLE: IL-6-inducible complexes on an IL-6 response element of the junB promoter contain Stat3 and 36 kDa CRE-like site binding protein(s.
AUTHOR(S): Kojima, Hirotada; Nakajima, Koichi; Hirano, Toshio (1)
CORPORATE SOURCE: (1) Dep. Mol. Oncol., Biomedical Res. Cent., Osaka University Medical School, Suita, Osaka 565 Japan
SOURCE: Oncogene, (1996) Vol. 12, No. 3, pp. 547-554.
ISSN: 0950-9232.
DOCUMENT TYPE: Article
LANGUAGE: English

AB The junB gene is one of immediate-early genes whose expression are regulated by a variety of extracellular stimuli and play important roles in cellular responses to the given stimuli. Interleukin-6 (IL-6) activates the junB promoter through an IL-6 response element, JRE-IL6, that is composed of two cooperative DNA motifs, a low affinity Stat-binding site overlapping with an Ets-binding site (JEBS) and a cAMP responsive element (CRE)-like site. This element is a target for the Jak-Stat signal transduction pathway. We showed that IL-6 induced novel complexes on JRE-IL6, termed JRE-IL6-BC1 and 2, which contained Stat3 but migrated more slowly than the complexes containing homo- or heterodimer of Stat3 and Stat1 in gel shift assays. These slow-migrating JRE-IL6-BCs appeared to contain CRE-like site binding proteins besides Stat3, since the formation of JRE-IL6-BCs required both the JEBS and CRE-like site of JRE-IL6 and **oligonucleotides** containing the CRE-like site or **somatostatin** CRE efficiently competed with JRE-IL6 for making JRE-IL6-BCs. The formation of the complexes correlated well with the responsiveness of JRE-IL6 to IL-6 signals. U.v.-cross **linking** study revealed that JRE-IL6 bound a 90 kDa protein, corresponding to

Stat3, and a 36 kDa protein, most likely a CRE-like site binding protein(s). Furthermore, we showed that the IL6/interferon-gamma (IFN-gamma) response element in the IRF-1 promoter (IR/IRF-1), which contains a Stat-binding site and an adjacent CRE-like site, also makes IL-6-induced binding complexes similar to JRE-IL6-BCs.

L9 ANSWER 6 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1994:409030 BIOSIS
DOCUMENT NUMBER: PREV199497422030
TITLE: Molecular cloning and expression of a pituitary **somatostatin** receptor with preferential affinity for **somatostatin**-28.
AUTHOR(S): O'Carroll, Anne-Marie (1); Lolait, Stephen J.; Konig, Monika; Mahan, Lawrence C.
CORPORATE SOURCE: (1) Lab. Cell Biol., Build. 36, Room 3A-17, Natl. Inst. Health, 9000 Rockville Pike, Bethesda, MD 20892 USA
SOURCE: Molecular Pharmacology, (1992) Vol. 42, No. 6, pp. 939-946. ISSN: 0026-895X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Using the polymerase chain reaction technique with degenerative primers, we obtained from a rat pituitary cDNA library a cDNA fragment, rAP236, that exhibited considerable homology to known receptors that belong to the guanine nucleotide-binding protein (G protein)-coupled receptor superfamily. **Oligonucleotides** to this fragment were used as probes to obtain a full-length cDNA from the rat pituitary cDNA library. This clone, rAP6-26, encoded a 383-amino acid protein with seven putative transmembrane domains that are characteristic of G protein-coupled receptors. The predicted amino acid sequence of the rAP6-26 cDNA exhibits 56-66% homology to recently cloned **somatostatin** (SRIF) receptors. Membranes prepared from COS-7 cells transfected with the rAP6-26 cDNA showed specific binding of 125I-Tyr-11-SRIF, thus identifying the cDNA clone as a novel SRIF receptor. Radioligand binding competition analysis using **somatostatin**-28 (SRIF-28) and a number of cyclic SRIF analogs revealed that SRIF-28 was the most potent competitor of 125I-Tyr-11-SRIF binding, with a apprx 30-fold greater affinity for the receptor than that of SRIF. In addition, binding of 125I-Tyr-11-SRIF was markedly reduced in the presence of Na+ ions and GTP, indicating coupling of rAP6-26 receptors to inhibitory G proteins in COS-7 membranes. In adenylyl cyclase assays, forskolin-induced cAMP accumulation was inhibited by SRIF and SRIF-28, thus confirming that the rAP6-26 cDNA encodes a functional receptor protein. By Northern blot analysis, a apprx 2.6 kilobase mRNA encoding the receptor was present in the pituitary but not in the liver, small intestine, kidney, pancreas, cerebellum, or cortex. Lack of receptor mRNA expression in the brain was confirmed by in situ hybridization histochemical studies. Thus, we report the cloning of a novel rat pituitary SRIF receptor, termed SSTR4, that has marked preferential affinity for SRIF-28 and is **linked** to inhibition of adenylyl cyclase.

L9 ANSWER 7 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1989:357083 BIOSIS
DOCUMENT NUMBER: BA88:49197
TITLE: **SOMATOSTATIN** GENE EXPRESSION IN PANCREATIC ISLET CELLS IS DIRECTED BY CELL-SPECIFIC DNA CONTROL ELEMENTS AND DNA-BINDING PROTEINS.
AUTHOR(S): POWERS A C; TEDESCHI F; WRIGHT K E; CHAN J S; HABENER J F
CORPORATE SOURCE: LAB. MOL. ENDOCRINOL., MASSACHUSETTS GENERAL HOSP. AND HOWARD HUGHES MED. INST., HARVARD MED. SCH., BOSTON, MASS. 02114.
SOURCE: J BIOL CHEM, (1989) 264 (17), 10048-10056. CODEN: JBCHA3. ISSN: 0021-9258.

FILE SEGMENT: BA; OLD
LANGUAGE: English
AB **Somatostatin** is a peptide synthesized in the pancreatic islets, nervous system, gastrointestinal tract, and thyroid gland. Factors that control islet cell-specific expression of the **somatostatin** gene were analyzed by expression of fusion genes consisting of 5' rat **somatostatin** gene sequences **linked** to coding sequences of the reported genes, bacterial chloramphenicol acetyltransferase, and human growth hormone. Fusion genes containing 900 and 250 base pairs (bp) of 5'-flanking DNA were preferentially expressed at 5-10-fold higher levels in **somatostatin**-producing islet cell lines, as compared with islet cell lines that produced insulin and glucagon, and in three non-islet cell lines. A deletional mutation consisting of only 65 bp of 5'-flanking sequence of the rat **somatostatin** gene expressed in all islet cell lines but not in non-islet lines, indicating the existence of a negative-acting islet cell-specific element located between nucleotides-250 and -65. The 65-bp sequence contains the octameric cAMP-responsive enhance (CRE) TGACGTCA (nucleotides- 48 to -41). Fine mapping of sequences responsible for islet-specific expression by substitution of synthetic **oligonucleotide** cassettes revealed full retention of expression by deletion to nucleotides -48 and complete loss of exprssion at nucleotides -42 of the CRE. Substitution of the 9 bp adjacent 3' to the CRE of the **somatostatin** gene (nucleotides -40 to -32) with the corresponding sequence located 3' to the CRE of the glucagon gene abolished expression. By gel mobility shift and DNaseI footprinting analyses, proteins in extracts of islet cells bound to the 24 bp including the CRE and downstream adjacent 9 bp (nucleotides -58 to -35). An additional upstream region of DNA was protected from DNase I digestion (nucleotides -110 to -80). Proteins from non-islet cells bound to the region from nucleotides -58 to -35, but patterns of DNase I protection differed from those using proteins from islet cells. These observations indicate that several DNA-biding proteins interact with cis-acting elements located between 35 and 58 bp upstream of the transcriptional start site of the rat **somatostatin** gene to determine islet cell-specific gene expression. CRE-binding protein(s) is ubiquitous among phenotypically different cells, and expression of the **somatostatin** gene in nonsomatostatin-producing islet cells appears to be inhibited by a negative-acting element located upstream of the CRE.

L9 ANSWER 8 OF 27 MEDLINE
ACCESSION NUMBER: 95188877 MEDLINE
DOCUMENT NUMBER: 95188877 PubMed ID: 7882976
TITLE: Two amino acids, located in transmembrane domains VI and VII, determine the selectivity of the peptide agonist SMS 201-995 for the SSTR2 **somatostatin** receptor.
AUTHOR: Kaupmann K; Bruns C; Raulf F; Weber H P; Mattes H; Lubbert H
CORPORATE SOURCE: Preclinical Research 386-226, Sandoz Pharma Ltd, Basel, Switzerland.
SOURCE: EMBO JOURNAL, **(1995 Feb 15)** 14 (4) 727-35.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199504
ENTRY DATE: Entered STN: 19950425
Last Updated on STN: 19960129
Entered Medline: 19950407
AB Human **somatostatin** receptor subtypes (SSTR1-5) bind their natural ligands SRIF-14 and SRIF-28 with high affinity. By contrast, short synthetic SRIF analogues such as SMS 201-995, a peptide agonist used for

the treatment of various endocrine and malignant disorders, display sub-nanomolar affinity only for the receptor subtype SSTR2. To understand the molecular nature of selective peptide agonist binding to **somatostatin** receptors we have now, by site-directed mutagenesis, identified amino acids mediating SMS 201-995 specificity for SSTR2. Sequentially, amino acids in SSTR1, a receptor subtype exhibiting low affinity for SMS 201-995, were exchanged for the corresponding SSTR2 residues. After three consecutive steps, in which eight amino acids were exchanged, a SSTR1 mutant receptor with high affinity for SMS 201-995 was obtained. Receptor mutants with different combinations of these eight amino acids were then constructed. A single Ser305 to Phe mutation in TM VII increased the affinity of SSTR1 for SMS 201-995 nearly 100-fold. When this mutation was combined with an exchange of Gln291 to Asn in TM VI, almost full susceptibility to SMS 201-995 was obtained. Thus, it is concluded that the specificity of SMS 201-995 for SSTR2 is mainly defined by these two amino acids in transmembrane domains VI and VII. Using the **conjugate** gradient method we have, by analogy to the well established structure of bacteriorhodopsin, built a model for SRIF receptor-ligand interactions that explains the importance of Gln291 and Ser305 for the selectivity of agonists.

L9 ANSWER 9 OF 27 MEDLINE

ACCESSION NUMBER: 94305906 MEDLINE
DOCUMENT NUMBER: 94305906 PubMed ID: 8032684
TITLE: An activator element within the preprotachykinin-A promoter.
AUTHOR: Morrison C F; McAllister J; Dobson S P; Mulderry P K; Quinn J P
CORPORATE SOURCE: MRC Brain Metabolism Unit, Royal Edinburgh Hospital, United Kingdom.
SOURCE: MOLECULAR AND CELLULAR NEUROSCIENCES, **(1994 Apr)** 5 (2) 165-75.
Journal code: 9100095. ISSN: 1044-7431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 19940825
Last Updated on STN: 19970203
Entered Medline: 19940816

AB The rat Preprotachykinin-A promoter (PPT) directs high levels of expression in dorsal root ganglia (DRG) neurons in culture either endogenously or when **linked** to a receptor construct. It is not active in any of the established tissue culture cell lines which we have analyzed. To search for transcriptional regulators within this promoter we have started to dissect the promoter into individual elements to determine their function. A DNA element which had previously been suggested to regulate transcription from DNA sequence analysis of the rat PPT promoter occurs at position -200 relative to the major start of transcription within the PPT promoter. The equivalent element from the bovine PPT promoter had previously been proposed to be a cAMP responsive element (CRE). The sequence of this enhancer has similarities with both the AP1 and CRE DNA consensus sequences. We have demonstrated that one copy of this rat PPT element **linked** to a heterologous basal promoter will enhance transcription in HeLa and PC12 cell lines as well as adult rat DRG neurons grown in culture. It is also demonstrated that the rat PPT element will bind proteins in HeLa nuclear extract distinct from those binding to the well-characterized Gibbon Ape Leukemia Virus (GALV) AP1 or **somatostatin** CRE sites by gel retardation analysis. This PPT element, when cloned in a heterologous reporter construct, although showing properties of both AP1 and CRE elements, was functionally

distinguished from both the **somatostatin** CRE element and the GALV AP1 enhancer when these elements were tested in the same reporter construct. This PPT element has a constitutive level of activity in adult rat DRG neurons, which is fivefold higher than that driven by the reporter construct promoter. It is also significantly different from the same reporter construct **linked** to the **somatostatin** CRE and analyzed in DRG neurons.

L9 ANSWER 10 OF 27 MEDLINE
ACCESSION NUMBER: 90384401 MEDLINE
DOCUMENT NUMBER: 90384401 PubMed ID: 1976223
TITLE: Mechanism of action of **somatostatin**: an overview of receptor function and studies of the molecular characterization and purification of **somatostatin** receptor proteins.
AUTHOR: Patel Y C; Murthy K K; Escher E E; Banville D; Spiess J; Srikant C B
CORPORATE SOURCE: Department of Medicine, McGill University-Royal Victoria Hospital, Montreal, Quebec, Canada.
CONTRACT NUMBER: ROI AM 21373 (NIADDK)
SOURCE: METABOLISM: CLINICAL AND EXPERIMENTAL, **(1990 Sep)** 39 (9 Suppl 2) 63-9.
Journal code: 0375267. ISSN: 0026-0495.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199010
ENTRY DATE: Entered STN: 19901122
Last Updated on STN: 19950206
Entered Medline: 19901019

AB To determine whether **somatostatin** receptor subtypes arise from molecular heterogeneity of the receptor protein, we have cross-**linked** the putative receptor in normal rat tissues and in AtT-20 and GH3 cells, both chemically with SS-14, SS-28 and Tyr3 SMS ligands, as well as by photoaffinity labeling with an azido derivative of Tyr3 SMS (EE 581). Three prominent **somatostatin** receptor proteins of 58-kDa, 32-kDa, and 27-kDa size have been identified. These proteins exhibit a tissue-specific distribution, ligand selectivity, and relative preference for SS-14 and SS-28 binding, and thus qualify as **somatostatin** receptor subtypes. Using EE 581 as a photoaffinity probe, the 58-kDa and 32-kDa proteins have been purified to homogeneity from brain and AtT-20 cells by successive SDS-PAGE. The 58-kDa form has been trypsinized and amino acid sequence data obtained from four tryptic fragments. With the help of synthetic **oligonucleotides** derived from these sequences, work is currently in progress to clone the 58-kDa protein to elucidate its complete sequence, its expression, and its functional relationship to the **somatostatin** receptor and its pharmacological subtypes.

L9 ANSWER 11 OF 27 MEDLINE
ACCESSION NUMBER: 90153971 MEDLINE
DOCUMENT NUMBER: 90153971 PubMed ID: 2137455
TITLE: Identification and purification of a novel 120-kDa protein that recognizes the cAMP-responsive element.
AUTHOR: Andrisani O; Dixon J E
CORPORATE SOURCE: Department of Biochemistry, Purdue University, West Lafayette, Indiana.
CONTRACT NUMBER: 18024
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, **(1990 Feb 25)** 265 (6) 3212-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199003
ENTRY DATE: Entered STN: 19900601
Last Updated on STN: 19970203
Entered Medline: 19900323

AB The TGACGTCA (CRE) motif required for function by a number of cellular (**somatostatin**, enkephalin, alpha-human chorionic gonadotropin) and viral (Ad5 E1A-inducible, HTLV-1 TAX-inducible) genes is the site of interaction of multiple sequence-specific complexes. A protocol has been developed for the fractionation and purification of these activities. We report here the purification from HeLa nuclear extracts of a novel 120-kDa polypeptide which by Southwestern blots, gel retardation, and UV cross-**linking** assays displays CRE-specific binding. The CRE-affinity purified 120-kDa protein displays properties distinct from those of the 43-kDa CREB/ATF polypeptide. The 120-kDa protein is readily phosphorylated in vitro by protein kinase C but not by protein kinase A, suggesting that this molecule may mediate cellular signals distinct from the cAMP-responsive pathway. In vitro transcription-complementation assays utilizing the purified 120-kDa protein failed to transactivate the cAMP-responsive **somatostatin** promoter suggesting that the mode of action of this 120-kDa polypeptide may require an activation step distinct from the cAMP-signaling pathway.

L9 ANSWER 12 OF 27 MEDLINE
ACCESSION NUMBER: 90007516 MEDLINE
DOCUMENT NUMBER: 90007516 PubMed ID: 2571562
TITLE: Use of variable simple sequence motifs as genetic markers: application to study of myotonic dystrophy.
AUTHOR: Smeets H J; Brunner H G; Ropers H H; Wieringa B
CORPORATE SOURCE: Department of Human Genetics, Radboud Hospital, University Nijmegen, The Netherlands.
SOURCE: HUMAN GENETICS, **(1989 Oct)** 83 (3) 245-51.
Journal code: 7613873. ISSN: 0340-6717.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198911
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 20000303
Entered Medline: 19891116

AB Among the many classes of repetitive elements present in the human genome, the ubiquitous "simple sequence motifs" (SSMs) composed of [A]n, [TG]n, [AG]n or codon-tandem repeats form a major source of genetic variation. Here we report a detailed molecular-genetic study of a "variable simple sequence motif" (VSSM) in the apolipoprotein C2 (apoC2) gene, which maps to the 19q13.2 region in the vicinity of the myotonic dystrophy (DM) locus. By combining in vitro DNA-amplification using the polymerase chain reaction and high-resolution gel electrophoresis, we could demonstrate a high degree of allelic variation with at least ten alleles, which differ in the number of repeated [TG] or [AG] dinucleotide units. Similar results were found for the **somatostatin** I gene locus. To evaluate the usefulness of SSM-length polymorphisms as genetic markers, the apoC2-VSSM was employed for **linkage** analysis in DM families. Our results establish that the orientation of the apolipoprotein gene cluster on 19q is cenapoE-apoC2-ter and indicate that the many thousands of structurally similar VSSMs in the human genome represent a rich source of highly informative genetic and diagnostic markers.

L9 ANSWER 13 OF 27 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 1998:273582 SCISEARCH
THE GENUINE ARTICLE: ZE691
TITLE: Co-stimulation of human peripheral blood mononuclear cells with IL-2 and anti-CD3 monoclonal antibodies induces phosphorylation of CREB
AUTHOR: Guyot D J; Newbound G C; Lairmore M D (Reprint)
CORPORATE SOURCE: OHIO STATE UNIV, DEPT VET BIOSCI, 1925 COFFEY RD, COLUMBUS, OH 43210 (Reprint); OHIO STATE UNIV, DEPT VET BIOSCI, COLUMBUS, OH 43210; OHIO STATE UNIV, CTR RETROVIRUS RES, COLUMBUS, OH 43210; OHIO STATE UNIV, ARTHUR JAMES CANC HOSP & RES INST, CTR COMPREHENS CANC, COLUMBUS, OH 43210
COUNTRY OF AUTHOR: USA
SOURCE: IMMUNOLOGY LETTERS, (**MAR 1998**) Vol. 61, No. 1, pp. 45-52.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0165-2478.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 47

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Phosphorylation of the cAMP-response element binding protein CREB within 1 h of CD2 but not CD3 cross-**linking** of human PBMC was recently demonstrated. The absence of P-CREB following CD3 cross-**linking** was unexpected, as other laboratories reported increased phosphorylation of CREB following CD3 cross-**linking** of the Jurkat lymphocyte cell line. Due to Jurkat T-cells being IL-2-independent, it was postulated that IL-2 might provide a necessary co-stimulus for phosphorylation of CREB in primary lymphocytes. Therefore, P-CREB was evaluated following co-stimulation of human PBMC through the IL-2 and CD2 or CD3 receptors. IL-2 did not further augment phosphorylation of CREB following CD2 cross-**linking**. However, while neither IL-2 nor CD3 cross-**linking** alone induced P-CREB, a 4.5-fold increase in phosphorylation of CREB within 1 h of IL-2/CD3 co-stimulation was observed. Phosphorylation was not associated with the induction of cAMP, and inhibition of PKA signaling had no effect on P-CREB. Consistent with signal transduction through p56(lck) or p59(fyn), inhibition of PTK signaling reduced phosphorylation 50%. Interestingly, inhibiting PKC signaling with calphostin C further increased P-CREB levels 3-fold over that observed in IL-2/CD3 co-stimulated cells not pretreated with a PKC inhibitor. In contrast to previous studies performed in the absence of exogenous IL-2, no increase in binding of CREB to a P-32-labeled **oligonucleotide** probe was observed by electrophoretic mobility shift assay. These data suggest that the IL-2 and CD3 signaling pathways provide a necessary and co-operative stimulus promoting phosphorylation of CREB following receptor cross-**linking**.

L9 ANSWER 14 OF 27 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 92:445533 SCISEARCH
THE GENUINE ARTICLE: JF088
TITLE: INTERACTION OF AP-1-LIKE, AP-2-LIKE, AND SP1-LIKE PROTEINS WITH 2 DISTINCT SITES IN THE UPSTREAM REGULATORY REGION OF THE PLASMINOGEN-ACTIVATOR INHIBITOR-1 GENE MEDIATES THE PHORBOL 12-MYRISTATE 13-ACETATE RESPONSE
AUTHOR: DESCHEEMAEKER K A; WYNS S; NELLES L; AUWERX J; NY T; COLLEN D (Reprint)
CORPORATE SOURCE: CATHOLIC UNIV LEUVEN, CTR THROMBOSIS & VASC RES, CAMPUS GASTHUISBERG, B-3000 LOUVAIN, BELGIUM; CATHOLIC UNIV LEUVEN, LEGENDO, B-3000 LOUVAIN, BELGIUM; UMEA UNIV, APPL

CELL & MOLEC BIOL UNIT, S-90187 UMEA, SWEDEN
COUNTRY OF AUTHOR: BELGIUM; SWEDEN
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (**25 JUL 1992**) Vol. 267, No. 21, pp. 15086-15091.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 39

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Phorbol 12-myristate 13-acetate induces a 3- and 10-fold induction of chloramphenicol acetyltransferase (CAT) activity in HT1080 and HeLa cells, respectively, following transient transfection of a 336-base pair plasminogen activator inhibitor-1 (PAI-1) promoter fragment **linked** to a CAT reporter gene. Substitution mutations in the regions encompassing nucleotides -78 to -69 (TGGGTGGGGC) or -61 to -54 (TGAGTTCA), but not in the regions -155 to -149 (TGCCTCA) or -84 to -76 (AGTGAGTGG) reduced this induction. Gel electrophoresis of double-stranded -65 to -50 **oligonucleotides** of the PAI-1 promoter region and nuclear extracts from Hela cells produced a gel shift pattern similar to that obtained with a AP-1 consensus oligomer, and excess unlabeled AP-1 oligomer reverted binding, suggesting that this region of the PAI-1 promoter is an AP-1-like binding site. Gel electrophoresis of double-stranded -82 to -65 **oligonucleotides** with HeLa nuclear extracts revealed a gel shift pattern of three bands; Sp1 consensus oligomer competed with the binding to two of these bands and AP-2 consensus sequence oligomer with the binding to the third band. The -82 to -65 oligomer also bound to purified AP-2 and Sp1 proteins. Southwestern blotting of HeLa nuclear extracts revealed that the labeled oligomer spanning region -82 to -65 bound to proteins with molecular masses of 52 and 72 kDa. Consensus AP-2 **oligonucleotides** competed for binding of the labeled -82 to -65 **oligonucleotide** to the 52-kDa protein, but consensus Sp-1 **oligonucleotides** did not compete for binding to the 72-kDa compound. The 72-kDa component binding to the -82 to -65 region may represent a new protein involved in transcriptional regulation.

L9 ANSWER 15 OF 27 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 92:304415 SCISEARCH
THE GENUINE ARTICLE: HT463
TITLE: SEQUENCES THAT DIRECT RAT TYROSINE-HYDROXYLASE GENE-EXPRESSION
AUTHOR: FUNG B P; YOON S O; CHIKARAISHI D M (Reprint)
CORPORATE SOURCE: TUFTS UNIV, SCH MED, NEUROSCI PROGRAM, 136 HARRISON AVE, BOSTON, MA, 02111; TUFTS UNIV, SCH MED, DEPT MICROBIOL & MOLEC BIOL, BOSTON, MA, 02111
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF NEUROCHEMISTRY, (**JUN 1992**) Vol. 58, No. 6, pp. 2044-2052.
ISSN: 0022-3042.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 50

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Investigation of neuroendocrine genes has revealed that transcription is regulated via multiple DNA binding sites, including the cyclic AMP response element (CRE). We show here that for the neuronal and chromaffin-specific gene tyrosine hydroxylase (TH), a 70-bp region (-229 to -160) lacking the CRE is sufficient, in either orientation, to confer levels of chloramphenicol acetyltransferase reporter expression equivalent to or greater than that conferred by 4.8 kb of the rat TH enhancer/promoter region. The 70-bp region contains potential binding

sites for AP2, AP1, E2A/MyoD, and POU transcription factors, and functions when **linked** to the TH promoter, but not when joined to a heterologous RSV promoter. This demonstrates that promoter as well as enhancer elements are important for TH expression. In gel-shift assays, the 70-bp fragment forms a cell type-specific complex with nuclear extracts from TH-expressing cells, which is effectively competed by an **oligonucleotide** containing AP2, AP1, and E2A/MyoD (E box) sites, but not by one containing the POU site. These data suggest that the AP2, AP1, and/or E box sites may be involved in forming the cell-specific complex. Although it lacks an authentic CRE, the 70-bp region also mediated a twofold transcriptional response to forskolin, equivalent to that found with the endogenous gene. A different region (-60 to -29) bearing a consensus CRE mediated a sixfold increase in transcription in response to forskolin, but only minimally activated basal transcription from the TH promoter in the absence of forskolin.

L9 ANSWER 16 OF 27 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 91:267147 SCISEARCH
THE GENUINE ARTICLE: FK114
TITLE: REGULATION OF THE ALPHA-INHIBIN GENE BY CYCLIC ADENOSINE-3',5'-MONOPHOSPHATE AFTER TRANSFECTION INTO RAT GRANULOSA-CELLS
AUTHOR: PEI L (Reprint); DODSON R; SCHODERBEK W E; MAURER R A; MAYO K E
CORPORATE SOURCE: NORTHWESTERN UNIV, DEPT BIOCHEM, EVANSTON, IL, 60208 (Reprint); NORTHWESTERN UNIV, DEPT MOLEC BIOL, EVANSTON, IL, 60208; NORTHWESTERN UNIV, DEPT CELL BIOL, EVANSTON, IL, 60208; UNIV IOWA, DEPT PHYSIOL & BIOPHYS, IOWA CITY, IA, 52242
COUNTRY OF AUTHOR: USA
SOURCE: MOLECULAR ENDOCRINOLOGY, (**1991**) Vol. 5, No. 4, pp. 521-534.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 60

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Inhibin gene expression in the ovary is stimulated by FSH, which uses cAMP as an intracellular second messenger. To examine further the transcriptional regulation of the alpha inhibin gene by FSH and cAMP, we have isolated and characterized a genomic clone that contains the entire rat alpha inhibin gene. Sequence analysis of the alpha inhibin promoter region revealed several potential cAMP response elements (CREs) and transcription factor AP2-binding sites that might mediate cAMP regulation. To determine the functional importance of these sequences, fusion genes including the alpha inhibin 5' flanking region **linked** to a luciferase reporter gene were transiently transfected into primary granulosa cells isolated from immature rats. These fusion genes were both expressed and regulated by the adenylyl cyclase activator forskolin in transfected granulosa cells. Analysis of a series of 5' deletion mutants indicated that a construct containing as little as 170 basepairs up-stream of the alpha inhibin start site, which includes a single imperfect CRE and no AP2 sites, was regulated by forskolin. DNAse footprinting was used to demonstrate that bacterially expressed CRE-binding protein (CREB) binds to this CRE located 122 base-pairs up-stream of the alpha inhibin gene transcriptional start site. To investigate further the role of this CRE in alpha inhibin gene expression, site-specific mutagenesis of the CRE was performed. The alpha inhibin promoter containing a mutated CRE was not regulated by forskolin in granulosa cells and did not bind the CREB protein. Interestingly, mutation of the CRE also substantially reduced basal expression of the alpha inhibin promoter. Lastly, a gel mobility shift assay was used to examine CRE-binding proteins from granulosa cell

extracts. Granulosa cells contain a protein that specifically interacts with CRE-containing **oligonucleotides** or with the alpha inhibin promoter and that is recognized by antibodies against the CREB protein. Our results suggest that CREB or related transcription factors play an important role in both basal and cAMP-regulated expression of the alpha inhibin gene in ovarian granulosa cells.

L9 ANSWER 17 OF 27 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 135:251986 CA
TITLE: Methods for treating fibroproliferative diseases with antiproliferative or antifibrotic agents, especially **antisense** c-Jun **oligonucleotides**
INVENTOR(S): Peterson, Theresa C.
PATENT ASSIGNEE(S): Dalhousie University, Can.
SOURCE: U.S., 13 pp., Cont.-in-part of U.S. 6,025,151.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
US 6294350	B1	20010925	US 1999-433621	19991102	
US 5985592	A	19991116	US 1997-870096	19970605	<--
US 6025151	A	20000215	US 1998-92317	19980605	<--
WO 2001032156	A2	20010510	WO 2000-IB1731	20001102	

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1997-870096 A2 19970605
US 1998-92317 A2 19980605
US 1999-433621 A1 19991102

AB In accordance with the present invention, fibroproliferative disease or condition characterized by such symptoms as increased levels of c-Jun homodimers, increased heterodimerization of c-Jun with another signaling peptide, increased levels of phosphorylated c-Jun, or increased presence of Jun kinase are treated by administering to the subject an amt. of a compd. effective to ameliorate one or more of the symptoms of the disease or condition, for example, an antiproliferative or antifibrotic agent. Preferred compds. for administration according to the invention are **antisense** c-Jun **oligonucleotides** and compds. that block c-Jun phosphorylation, such as pentoxifylline, or a functional deriv. or metabolite thereof. Also provided by the present invention are in vitro tests for identifying whether a test compd. is useful for treatment of a subject afflicted with such a disease and kits useful for conducting such assays.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 18 OF 27 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 134:25369 CA
TITLE: **Oligonucleotides** for inhibition of gastric acid production and/or secretion
INVENTOR(S): Tachas, George
PATENT ASSIGNEE(S): Australia

SOURCE: PCT Int. Appl., 164 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 2000071164	A1	20001130	WO 2000-AU498	20000524	<--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
EP 1185303	A1	20020313	EP 2000-926576	20000524	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					

PRIORITY APPLN. INFO.: AU 1999-510 A 19990524
WO 2000-AU498 W 20000524

AB Methods are provided for the treatment or prevention of gastric acid disturbances and for reducing the breakdown of acid sensitive agents in the gastrointestinal tract. Also provided is a method for transfecting parietal cells in vivo. Synthetic **oligonucleotides** are provided which may be used in these methods.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 19 OF 27 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 132:105019 CA
TITLE: Synthesis and identification of bivalent binding RNA molecules to G protein-coupled receptors
INVENTOR(S): Gold, Larry
PATENT ASSIGNEE(S): Nexstar Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 2000004184	A1	20000127	WO 1999-US14853	19990630	<--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
AU 9947287	A1	20000207	AU 1999-47287	19990630	<--
EP 1100960	A1	20010523	EP 1999-930840	19990630	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					

PRIORITY APPLN. INFO.: US 1998-118525 A 19980717
WO 1999-US14853 W 19990630

AB Methods for identifying and prepg. bivalent binding mols. to 7 transmembrane domain contg. G protein-coupled receptors are described. The methods are based on the SELEX method (Systematic Evolution of Ligands by EXponential enrichment) for generating high affinity nucleic acid ligands, termed aptamers. It combines two or more binding domains to two or more different epitopes of the same 7 transmembrane G protein-coupled receptor. The method was exemplified by screening in the random RNA library for binding mols. to either ECL1 (extracellular loop 1) or ECL2 of neurokinin receptor NK1R using peptide affinity columns. The bivalent ligands, derived from two ECL1- and ECL1-binding RNA libraries by **linking** them through overlap-extension PCR reaction, can be enriched after cycles of SELEX process to generate double-stranded DNA templates for their future synthesis . These bivalent binding mols. may be useful as therapeutic and diagnostic agents.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 20 OF 27 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 128:208915 CA
TITLE: Methods for the production of protein particles useful for delivery of pharmacological agents
INVENTOR(S): Magdassi, Shlomo; Desai, Neil; Ferreri, Kevin; Soon-Shiong, Patrick
PATENT ASSIGNEE(S): Vivorx Pharmaceuticals, Inc., USA; Magdassi, Shlomo; Desai, Neil; Ferreri, Kevin; Soon-Shiong, Patrick
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9807410	A1	19980226	WO 1997-US14661	19970819 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9739169	A1	19980306	AU 1997-39169	19970819 <--
EP 938299	A1	19990901	EP 1997-936517	19970819 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1996-23968P P 19960819
WO 1997-US14661 W 19970819

AB A method has been developed for the formation of submicron particles (nanoparticles) by heat-denaturation of proteins (such as human serum albumin) in the presence of multivalent ions (such as calcium). Also provided are novel products produced by the invention method. An appropriate concn. of multivalent ions, within a relatively narrow range of concns., induces the pptn. of protein in the form of colloidal particles, at a temp. which is well below the heat denaturation temp. of the protein (as low as 60 .degree.C for serum albumin). Temps. at which invention method operates are sufficiently low to permit incorporation of other mols. (e.g., by co-pptn.), into submicron particles according to the invention, including compds. which cannot withstand high temps. Invention methods facilitate the prodn. of protein nanoparticles and microparticles contg. various mols. (such as nucleic acids, **oligonucleotides,**

polynucleotides, DNA, RNA, polysaccharides, ribozymes, pharmacol. active compds., and the like) useful for therapeutic, diagnostic and other purposes. The addn. of multivalent cations serves both to induce pptn., and to allow **linking** of neg. charged mols., such as DNA, to the neg. charged protein. Microparticles and nanoparticles were formed from albumin in the presence of CaCL2.

L9 ANSWER 21 OF 27 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 126:127158 CA
TITLE: **Somatostatin** receptor subtypes in human astrocytes and gliomas: Influence of cultivation process
AUTHOR(S): Feindt, J.; Hugo, H. -H.; Mentlein, R.; Krisch, B.
CORPORATE SOURCE: Universitat Kiel, Anatomisches Institut, Kiel, D-24098, Germany
SOURCE: Peptidergic Neuron, [International Symposium on Neurosecretion] 12th, Kiel, Sept. 20-22, 1995 (**1996**), Meeting Date 1995, 141-150. Editor(s): Krisch, Brigitte; Mentlein, Rolf. Birkhaeuser: Basel, Switz.
CODEN: 63XVA3
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Expression of **somatostatin** receptors was investigated on normal human astrocytes and human glial tumors. All cultivated glial cells and gliomas, directly embedded in paraffin were immunopos. for the astrocytic marker glial fibrillary acidic protein. Moreover, **somatostatin** -binding sites could be visualized on all cell types of affinity labeling with a **somatostatin**-gold **conjugate**. Thereby, the normal astrocytes showed a fine, stippled pattern of the **conjugate** all over the cell surface whereas the tumorous cells had a more thread-like pattern preferentially on the cell processes. The transcripts of the different **somatostatin** receptor subtypes were detected by reverse transcription - polymerase chain reaction (RT-PCR) with **oligonucleotides** specific for five human **somatostatin** receptor subtypes (SSTRs). Normal astrocytes expressed SSTR-1, (SSTR-2) and SSTR-4 specific transcripts, glioma cells showed an overexpression of SSTR-2 compared to normal astrocytes (relative to equal intensities for .beta.-actin amplificates). This overexpression of SSTR-2 transcript could be detected in cultivated tumor glial cells as well as in solid gliomas. Thus, the cultivation process had no influence on the individual SSTR-2 expression on normal and tumorous cells.

L9 ANSWER 22 OF 27 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 121:149949 CA
TITLE: Heterologous expression and purification of anglerfish **somatostatin** precursors in Escherichia coli
AUTHOR(S): Kang, Jung Seog; Lee, Myung Ae; Park, Sang Dai; Hong, Seung Hwan
CORPORATE SOURCE: Coll. Nat. Sci., Seoul Natl. Univ., Seoul, 151-742, S. Korea
SOURCE: Mol. Cells (**1994**), 4(1), 91-7
CODEN: MOCEEK; ISSN: 1016-8478
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To investigate the structure-function relationship of the pro-region in mediating tissue-specific cleavage of peptide hormone precursors, prosomatostatins (proSRIFs) from anglerfish (Lophius americanus) were overexpressed in E. coli and purified. The cDNAs of preproSRIF I and II genes from the anglerfish were inserted into the E. coli glutathione S-transferase (GST) fusion vector, pGEX-3X, and periplasmic secretion vector, pIN-III-ompA2, resp. By **oligonucleotide**-directed

mutagenesis using a polymerase chain reaction, the **linker** region, 5'-untranslated sequence, and signal peptide were deleted. When cells harboring these constructs were induced with 1 mM IPTG, GST-proSRIF I of 38 kDa and proSRIF II of 14 kDa were overproduced. ProSRIF I protein fused to GST was purified by affinity chromatog. using glutathione Sepharose 4B, followed by cleavage of GST fusion protein with activated factor X. ProSRIF II protein was purified first by collecting the periplasmic fraction after osmotic shock and then through the conventional column chromatog. methods. These purified pro-hormone peptides can be used to crystallize and det. their tertiary structures.

L9 ANSWER 23 OF 27 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 120:262321 CA
TITLE: Receptor identification method
INVENTOR(S): Hadcock, John Richard; Ozenberger, Bradley Alton; Pausch, Mark Henry
PATENT ASSIGNEE(S): American Cyanamid Co., USA
SOURCE: Eur. Pat. Appl., 17 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
EP 578962	A2	19940119	EP 1993-108984	19930604	<--
EP 578962	A3	19941026			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE					
US 5668006	A	19970916	US 1992-915966	19920717	<--
JP 06153954	A2	19940603	JP 1993-195229	19930713	<--
CA 2100616	AA	19940118	CA 1993-2100616	19930715	<--
AU 9342034	A1	19940120	AU 1993-42034	19930716	<--
AU 667374	B2	19960321			
ZA 9305173	A	19940302	ZA 1993-5173	19930716	<--
US 5929209	A	19990727	US 1996-771182	19961220	<--
US 6077666	A	20000620	US 1997-853194	19970508	<--

PRIORITY APPLN. INFO.: US 1992-915966 A 19920717
AB A method for isolating and cloning the DNA sequences encoding the receptors such as the superfamily of G protein-**linked** receptors is disclosed. Isolation of a DNA sequences encoding a novel **somatostatin** receptor subtype SSTR3 by PCR is described..

L9 ANSWER 24 OF 27 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 109:206059 CA
TITLE: Structural determinants for transcriptional activation by cAMP-responsive DNA elements
AUTHOR(S): Deutsch, Paul J.; Hoeffler, James P.; Jameson, J. Larry; Lin, Julia C.; Habener, Joel F.
CORPORATE SOURCE: Lab. Mol. Endocrinol., Massachusetts Gen. Hosp., Boston, MA, 02114, USA
SOURCE: J. Biol. Chem. (**1988**), 263(34), 18466-72
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A transcriptional cAMP-responsive enhancer element (CRE) consisting of the 8-base-pair (bp) palindrome, 5'TGACGTCA 3', is found in several eukaryotic genes. The effects on gene transcription of point mutations within the CRE, the influence of the bases surrounding the CRE, and the requirements for transcriptional synergism of tandemly repeated CREs were studied. When inserted as an **oligonucleotide** with restriction enzyme **linker** sites, the 8-bp CRE itself is as active in conferring cAMP

responsivity on an enhancerless chloramphenicol acetyltransferase reporter plasmid as is a single copy of the choriogonadotropin .alpha. (CG.alpha.), twice repeated 18-bp sequence contg. the CRE. Point mutations in the first (T to A), fourth (C to G), or eighth (A to T) positions of the CRE, when contained within the CG.alpha. 18-bp sequence, each inhibited transcriptional activity >90%. However, the identical eighth position A .fwdarw. T mutation occurs in the cAMP-responsive sequence of the vasoactive intestinal peptide (VIP) gene, and that mutant sequence in the context of the adjacent bases of the native VIP sequence is maximally cAMP responsive when inserted in the reporter plasmid. The substantially reduced activity of the core 8-bp CRE when synthesized as a cassette including the adjacent bases of the rat glucagon or bovine parathyroid hormone gene further emphasizes the restrictive influence of particular surrounding sequences. Active **oligonucleotides** contg. the 8-bp palindrome and different but equally permissive contexts have comparable properties in transfected reporter genes and gel mobility-shift assays. The pair of tandemly repeated 18-bp elements contg. the CRE in the CG.alpha. gene synergistically stimulate transcription either with paired native CREs or when 1 native CRE is paired with 1 mutant CRE, suggesting the presence of cooperative interactions. Tandem insertion of more than two 18-bp sequences, or insertion of addnl. sequences between the 2 CREs, inhibits transcription. These observations indicate that the contexts of the bases adjacent to CREs exert profound influences on the transcriptional activities mediated by the cAMP-responsive elements.

L9 ANSWER 25 OF 27 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 106:170241 CA
TITLE: Bacterial polypeptide expression employing tryptophan promoter-operator
INVENTOR(S): Kleid, Dennis G.; Yansura, Daniel G.; Heyneker, Herbert L.; Miozzari, Giuseppe F.
PATENT ASSIGNEE(S): Genentech, Inc., USA
SOURCE: Can., 50 pp. Division of Can. Appl. No. 373,565.
CODEN: CAXXA4
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
CA 1213539	A2	19861104	CA 1985-482003	19850521	<--
CA 1198068	A1	19851217	CA 1981-373565	19810320	<--
IL 71885	A1	19860131	IL 1981-71885	19810323	<--
AT 52802	E	19900615	AT 1985-100548	19810323	<--
US 4663283	A	19870505	US 1983-543682	19831020	<--
FI 8503488	A	19850912	FI 1985-3488	19850912	<--
FI 8503489	A	19850912	FI 1985-3489	19850912	<--
FI 72344	B	19870130			
FI 72344	C	19870511			
US 5888808	A	19990330	US 1993-55960	19930429	<--
US 6333174	B1	20011225	US 1995-482321	19950606	

PRIORITY APPLN. INFO.:

US 1980-133296	A	19800324
CA 1981-373565	A3	19810320
FI 1981-876	A	19810320
EP 1985-100548	A	19810323
IL 1981-62460	A	19810323
US 1981-307473	A3	19811001
US 1984-685521	B1	19841224
US 1987-76253	B1	19870721
US 1989-345047	B1	19890427
US 1991-655215	B1	19910212

US 1991-773740 B1 19911009

AB A method for cleaving double-stranded DNA at any point, even in the absence of a restriction recognition site, is developed and used in the construction of expression plasmids contg. heterologous genes under the control of the trp promoter-operator lacking the attenuator for efficient expression in Escherichia coli without tryptophan starvation. The method comprises (1) converting the double-stranded DNA to single-stranded DNA in the region surrounding the intended cleavage point by reaction with .lambda. exonuclease; (2) hybridizing a DNA primer to the single-stranded DNA formed such that the 5' end of the primer is coterminus with the nucleotide on the single-stranded DNA just prior to the intended cleavage site; (3) extending the primer in the 3' direction with DNA polymerase; and (4) simultaneously or thereafter, digesting away the portion of the single-stranded DNA beyond the intended cleavage point. Plasmid pGM1 from which the trp attenuator region within the leader sequence had been deleted contained the trp promoter-operator (trp p.o.) region operatively **linked** to the codons for, from 5' to 3', the 1st 6 amino acids of the trp leader peptide (L), the distal regions of the trpE protein (E'), and the entire trpD protein (D). Construction of an expression vector carrying a **somatostatin**-trpLE' chimeric gene under the control of the trp p.o. was carried out by (1) excising from pGM1 the EcoRI-PvuII fragment carrying trp p.o., LE', and the 5' half of D (D'), and inserting the fragment in the EcoRI site of plasmid pSOMII carrying the **somatostatin** gene to obtain pSOM7.DELTA.2; with HindIII which cut at the 5' region of D'; (3) treating the linearized plasmid with .lambda. exonuclease until the single-stranded region extended beyond the 3' end of LE'; (4) hybridizing a primer having its 5' nucleotide complementary to the 3' nucleotide of LE' to the single-stranded region, and extending it using Klenow fragment; (5) digesting away the single-stranded region left with 3' to 5' exonuclease (6) excising the trp p.o.-LE' fragment with BglII, and converting the blunt 3' end of LE' to EcoRI site; and (7) ligating the fragment obtained in 6 to pSOM7.DELTA.2 having the BglII-EcoRI fragment excised, yielding plasmid pSOM7.DELTA.2.DELTA.4 with the entire D' deleted and with the **somatostatin** gene fused to LE' under the control of the trp p.o.

L9 ANSWER 26 OF 27 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 105:55690 CA
TITLE: Microbial polypeptide expression
INVENTOR(S): Itakura, Keiichi; Riggs, Arthur Dale
PATENT ASSIGNEE(S): Genentech, Inc., USA
SOURCE: Pat. Specif. (Aust.), 61 pp.
CODEN: ALXXAP
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
AU 546092	B2	19850815	AU 1981-74484	19810824 <--
AU 8174484	A1	19820114		

AB DNA encoding human **somatostatin** (I), preproinsulin, proinsulin, insulin A chain and insulin B chain or DNA encoding bovine or human growth hormone, LH, ACTH, and pancreatic polypeptide, and contg. a majority of codons preferred by microbial genomes, were synthesized from 11-mer-16mer **oligonuclotides** (obtained by the modified triester method of K. ltakura, et. al., 1975), by oligomer coupling and ligation of complementary synthetic strands using phage T4 ligase. The double-stranded DNA was inserted into a plasmid for expression in a microorganism. Thus, the synthetic I gene, modified by addn. of EcoRI and BamHI **linkers** and an ATG codon, was inserted in proper

orientation into the EcoRI-BamHI site of a plasmid pBR322 deriv. that contained a lac promoter and .beta.-galactosidase gene with an adjacent EcoRI site. The recombinant plasmid, pSOM11-13, was used to transform Escherichia coli RR1 and ampicillin resistant, .beta.-galactosidase colonies were selected by growth and blue color of colonies on ampicillin-contg. X-gal (5-bromo-4-chloroincolylgalactoside) indicator medium. E. coli RR1-pSOM11-3 colonies produced a fusion protein devoid of I activity but sufficiently large not to be degraded by E. coli proteinases and of such a size as to be acceptable in raising antibodies in animals. Cleavage of the fusion protein with CNBr (at the ATG-encoded methionines) resulted in I activity as demonstrated by cloned I binding to antibodies raised in rabbits by authentic I. The yield of I was low, but was improved by addn. to the medium of the lac operon inducer IPTG (isopropylthio-.beta.-D-galactoside). The I activity of E. coli RR1-pSOM11-3 ext. inhibited the release of growth hormone from rat pituitary cells. The activity derived from E. coli RR1-pSOM11-13 was enriched 100-fold by alc. extn. of the cleavage product and chromatog. on Sephadex G-50 in 50% AcOH. Substantially pure I was obtained by subsequent Sephadex G-50 chromatog. followed by HPLC. The methods for proper orientation of the synthetic DNA to obtain an easily detectable fusion protein and cleaved product with natural activity were applied to cloning other human and bovine hormone genes.

L9 ANSWER 27 OF 27 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 96:29414 CA
TITLE: A polypeptide product and a plasmidic expression vehicle for it, a method of creating an expression plasmid, a method of cleaving double stranded DNA, and specific plasmids
INVENTOR(S): Kleid, Dennis G.; Yansura, Daniel G.; Heyneker, Herbert L.; Miozzari, Giuseppe F.
PATENT ASSIGNEE(S): Genentech, Inc., USA
SOURCE: Eur. Pat. Appl., 51 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 36776	A2	19810930	EP 1981-301227	19810323 <--
EP 36776	A3	19821027		
EP 36776	B1	19880511		
R: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
ZA 8101368	A	19820428	ZA 1981-1368	19810302 <--
FI 8100876	A	19810925	FI 1981-876	19810320 <--
DK 8101299	A	19810925	DK 1981-1299	19810323 <--
DK 173085	B1	19991227		
NO 8100986	A	19810925	NO 1981-986	19810323 <--
BR 8101712	A	19810929	BR 1981-1712	19810323 <--
AU 8168636	A1	19811001	AU 1981-68636	19810323 <--
AU 542640	B2	19850228		
GB 2073203	A1	19811014	GB 1981-8986	19810323 <--
GB 2073203	B2	19840229		
FR 2480781	A1	19811023	FR 1981-5732	19810323 <--
FR 2480781	B1	19851018		
JP 56145221	A2	19811111	JP 1981-40529	19810323 <--
JP 07024582	B4	19950322		
DE 3111405	A1	19820325	DE 1981-3111405	19810323 <--
DE 3111405	C2	19900621		
ES 500617	A1	19820916	ES 1981-500617	19810323 <--

DD 159435	C	19830309	DD 1981-228534	19810323 <--
EP 86548	A2	19830824	EP 1983-200301	19810323 <--
EP 86548	A3	19831130		
EP 86548	B1	19870520		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
HU 27459	O	19831028	HU 1981-732	19810323 <--
HU 195534	B	19880530		
DD 203746	A5	19831102	DD 1981-243408	19810323 <--
DD 204494	A5	19831130	DD 1981-243409	19810323 <--
EP 154133	A2	19850911	EP 1985-100548	19810323 <--
EP 154133	A3	19860528		
EP 154133	B1	19900516		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
CS 238612	B2	19851216	CS 1981-2106	19810323 <--
CS 238645	B2	19851216	CS 1983-6230	19810323 <--
CS 238646	B2	19851216	CS 1983-6231	19810323 <--
IL 62460	A1	19860131	IL 1981-62460	19810323 <--
IL 71885	A1	19860131	IL 1981-71885	19810323 <--
AT 27306	E	19870615	AT 1983-200301	19810323 <--
AT 34183	E	19880515	AT 1981-301227	19810323 <--
AT 52802	E	19900615	AT 1985-100548	19810323 <--
DE 3153606	C2	19910425	DE 1981-3153606	19810323 <--
PL 147727	B1	19890731	PL 1981-252630	19810324 <--
PL 162227	B1	19930930	PL 1981-230296	19810324 <--
ES 509935	A1	19830316	ES 1982-509935	19820226 <--
ES 509936	A1	19830401	ES 1982-509936	19820226 <--
US 4663283	A	19870505	US 1983-543682	19831020 <--
AU 580959	B2	19890209	AU 1984-29964	19840627 <--
AU 8429964	A1	19841018		
AU 585832	B2	19890629	AU 1984-29963	19840627 <--
AU 8429963	A1	19841018		
NO 8403718	A	19810925	NO 1984-3718	19840918 <--
NO 161572	B	19890522		
NO 161572	C	19890830		
NO 8403719	A	19810925	NO 1984-3719	19840918 <--
NO 165644	B	19901203		
NO 165644	C	19910313		
FR 2555199	A1	19850524	FR 1984-19450	19841219 <--
FR 2555199	B1	19870904		
FI 8503488	A	19850912	FI 1985-3488	19850912 <--
FI 8503489	A	19850912	FI 1985-3489	19850912 <--
FI 72344	B	19870130		
FI 72344	C	19870511		
JP 05211885	A2	19930824	JP 1992-274165	19921013 <--
JP 06073469	B4	19940921		
JP 05268962	A2	19931019	JP 1992-274172	19921013 <--
JP 07034747	B4	19950419		
US 5888808	A	19990330	US 1993-55960	19930429 <--
US 6333174	B1	20011225	US 1995-482321	19950606

PRIORITY APPLN. INFO.:

US 1980-133296	A	19800324
FI 1981-876	A	19810320
EP 1981-301227	A	19810323
EP 1985-100548	A	19810323
IL 1981-62460	A	19810323
US 1981-307473	A3	19811001
US 1984-685521	B1	19841224
US 1987-76253	B1	19870721
US 1989-345047	B1	19890427
US 1991-655215	B1	19910212
US 1991-773740	B1	19911009

AB Plasmids are prepd. to contain (1) a linear double-stranded DNA fragment contg. a replicon and a gene which expresses a selectable characteristic

when placed under the control of a bacterial promoter, (2) a 2nd DNA fragment contg. a gene of a desired product, and (3) a 3rd DNA fragment contg. a bacterial promoter, with all 3 DNA fragments in the same reading frame. The activity of the gene in (2) is regulated by growing bacteria contg. the plasmids in media contg. appropriate concns. of an effector of the bacterial promoter (3). Thus, plasmid pBRHtrp was constructed by digesting the known plasmid pGM1, which contains an Escherichia coli tryptophan (trp) operon, with restriction endonuclease PvuII and joining **oligonucleotide linkers** to the PvuII fragment contg. the trp promoter-operator region. The **oligonucleotide linkers** contained recognition sites for restriction endonuclease EcoRI, which permitted insertion of the trp fragment into the EcoRI cleavage site of plasmid pBRH1 and ligation with phage T4 DNA ligase to give plasmid pBRHtrp. Plasmid pSOM7.DELTA.2, with a **somatostatin** gene under control of the trp promoter, was constructed by recovering the promoter-contg. DNA from pBRHtrp with endonuclease EcoRI and inserting the DNA into the EcoRI site of plasmid pSom11 (Itakura, K., et al., 1977). Escherichia coli Transformed with pSOM7.DELTA.2 formed a protein consisting of **somatostatin** fused to a short segment of the protein encoded by gene trpD. Formation of the fusion protein was repressed in media contg. high concns. of tryptophan. Immunol. reactive **somatostatin** was recovered from the fusion protein by CNBr cleavage.

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L2        226887 S OLIGONUCL? OR ANTISENSE
L3           771 S L1 AND L2
L4       1219308 S L3 AND CONJUGAT? OR LINK?
L5            56 S L3 AND (CONJUGAT? OR LINK?)
L6             2 S L1 (5N) (CONJUGAT? OR LINK?) (5N) (OLIGONUCL? OR ANTISENSE)
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L9            27 S L8 AND PY=<2000

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L10          337 EISENHUT, M?/AU


L11           73 MIER, W?/AU


L12            1 ERITIA, R?/AU


L13          411 HABERKORN, U?/AU

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L16  ANSWER 1 OF 9  BIOSIS  COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER:   2001:553169  BIOSIS
DOCUMENT NUMBER:    PREV200100553169
TITLE:              Preparation and preclinical development of tumor-targeting
                    peptide-PNA conjugates.
AUTHOR(S):          Mier, W. (1); Eritja, R.; Mohammed, A.;
                    Haberkorn, U.; Eisenhut, M.
CORPORATE SOURCE:   (1) Universitaetsklinikum, Heidelberg Germany
SOURCE:             Journal of Nuclear Medicine, (May, 2001) Vol. 42,
                    No. 5 Supplement, pp. 115P. print.
                    Meeting Info.: 48th Annual Meeting of the Society of
                    Nuclear Medicine Toronto, Ontario, Canada June 23-27, 2001
                    ISSN: 0161-5505.
DOCUMENT TYPE:      Conference
LANGUAGE:           English
SUMMARY LANGUAGE:   English

L16  ANSWER 2 OF 9  BIOSIS  COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER:   2001:549514  BIOSIS
DOCUMENT NUMBER:    PREV200100549514
TITLE:              68Ga-DOTA0-D PHE1-TYR3-octreotide (DOTATOC): A new
                    PET-ligand for imaging somatostatin receptors in
                    meningiomas.
AUTHOR(S):          Henze, M. (1); Schuhmacher, J.; Hipp, P.; Kowalski, J.;
                    Becker, D. W.; Maecke, H. R.; Debus, J.; Haberkorn,
                    U.
CORPORATE SOURCE:   (1) University of Heidelberg, Heidelberg Germany
SOURCE:             Journal of Nuclear Medicine, (May, 2001) Vol. 42,
                    No. 5 Supplement, pp. 67P. print.
                    Meeting Info.: 48th Annual Meeting of the Society of
                    Nuclear Medicine Toronto, Ontario, Canada June 23-27, 2001
                    ISSN: 0161-5505.
DOCUMENT TYPE:      Conference
LANGUAGE:           English
SUMMARY LANGUAGE:   English

L16  ANSWER 3 OF 9  BIOSIS  COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER:   2001:413723  BIOSIS
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DOCUMENT NUMBER: PREV200100413723
TITLE: PET imaging of **somatostatin** receptors using (68GA)DOTA-D-Phe1-Tyr3-octreotide: First results in patients with meningiomas.
AUTHOR(S): Henze, Marcus (1); Schuhmacher, Jochen; Hipp, Peter; Kowalski, Joerg; Becker, Dirk W.; Doll, Josef; Maecke, Helmut R.; Hofmann, Michael; Debus, Juergen; **Haberkorn, Uwe**
CORPORATE SOURCE: (1) Dept. of Nuclear Medicine, University of Heidelberg, Im Neuenheimer Feld 400, 69120, Heidelberg Germany
SOURCE: Journal of Nuclear Medicine, (**July, 2001**) Vol. 42, No. 7, pp. 1053-1056. print.
ISSN: 0161-5505.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Imaging of **somatostatin** receptors (SSTRs) using (111In)diethyl-enetriaminepentaacetic-acid-octreotide (DTPAOC) has proven to be helpful in the differentiation of meningiomas, neurinomas or neurofibromas, and metastases as well as in the follow-up of meningiomas. A drawback of the SPECT method is its limited sensitivity in detecting small meningiomas. Because of PET's increased spatial resolution and its ability to absolutely quantify biodistribution, a PET tracer for SSTR imaging would be desirable. Methods: 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic-acid-D-Phe1-Tyr3-octreotide (DOTATOC) was labeled using the positron-emitting generator nuclide 68Ga. We acquired dynamic PET images over 120 min after intravenous injection of 175 MBq (68Ga)DOTATOC in 3 patients suffering from 8 meningiomas (WHO Idegree; 7- to 25-mm diameter). Patients' heads had been fixed using individually shaped fiber masks equipped with an external stereotactic localizer system to match PET, CT, and MRI datasets. Results: (68Ga)DOTATOC was rapidly cleared from the blood (half-life alpha, 3.5 min; half-life beta, 63 min). Standardized uptake values (SUVs) of meningiomas increased immediately after injection and reached a plateau 60-120 min after injection (mean SUV, 10.6). No tracer could be found in the surrounding healthy brain tissue. All meningiomas (even the 3 smallest (7- to 8-mm diameter)) showed high tracer uptake and could be visualized clearly. Tracer boundaries showed a good correspondence with the matched CT and MRI images. PET provided valuable additional information regarding the extent of meningiomas located beneath osseous structures, especially at the base of the skull. Conclusion: According to our initial experiences, (68Ga)DOTATOC seems to be a very promising new PET tracer for imaging SSTRs even in small meningiomas, offering excellent imaging properties and a very high tumor-to-background ratio.

L16 ANSWER 4 OF 9 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:300098 BIOSIS
DOCUMENT NUMBER: PREV200100300098
TITLE: Tumor-targeting peptide-oligonucleotide conjugates.
AUTHOR(S): **Mier, W. (1)**; Eritja, R. (1); Mohammed, A. (1); **Haberkorn, U. (1); Eisenhut, M. (1)**
CORPORATE SOURCE: (1) Nuclear Medicine, Universitaetsklinikum Heidelberg, Heidelberg Germany
SOURCE: Journal of Cancer Research and Clinical Oncology, (2001) Vol. 127, No. Supplement 1, pp. S44. print.
Meeting Info.: Eleventh Congress of the Division of Experimental Cancer Research of the German Cancer Society Heidelberg, Germany April 04-06, 2001 German Cancer Society . ISSN: 0171-5216.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L16 ANSWER 5 OF 9 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:65051 BIOSIS
DOCUMENT NUMBER: PREV200100065051
TITLE: Preparation and evaluation of tumor-targeting peptide-oligonucleotide conjugates.
AUTHOR(S): **Mier, Walter (1)**; Eritja, Ramon; Mohammed, Ashour; **Haberkorn, Uwe**; **Eisenhut, Michael**
CORPORATE SOURCE: (1) Department of Nuclear Medicine, Universitaetsklinikum Heidelberg, INF 400, 69120, Heidelberg: walter_mier@med.uni-heidelberg.de Germany
SOURCE: Bioconjugate Chemistry, (**November December, 2000**) Vol. 11, No. 6, pp. 855-860. print.
ISSN: 1043-1802.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Enormous progress has been made in the development of antisense oligodeoxynucleotides (ODNs) as therapeutic agents inhibiting gene expression. Unfortunately, the therapeutical application of ODNs is still held back because of the low cellular uptake and the lack of specific transport into particular cells. In this paper, we report a drug-targeting system using **somatostatin** receptors (SSTRs) which are overexpressed in various tumors. Phosphorothioate ODNs were covalently linked to Tyr3-octreotate, an analogue of **somatostatin**. The peptide was assembled by solid-phase synthesis, oxidized to form the cyclic disulfide, and subsequently derivatized with a N-terminal maleimido functionality. 5'-Thiol derivatized phosphorothioate-ODNs directed against the protooncogene bcl-2 were conjugated to this maleimido-modified peptide. Binding studies revealed that the conjugates retain specific binding with nanomolar affinities to SSTRs (IC50-values between 1.83 and 2.52 nM). Furthermore, melting studies with complementary DNA revealed that the terminal conjugation of the ODNs did not significantly affect their hybridization affinity.

L16 ANSWER 6 OF 9 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:110898 BIOSIS
DOCUMENT NUMBER: PREV199698683033
TITLE: Efficient symptomatic control of carcinoid tumors with **somatostatin** in patients with disease progression under alpha-interferon therapy.
AUTHOR(S): Boehme, M. W.-J. (1); Schmidt-Gayk, H.; Bihl, H.; **Eisenhut, M.**; Herfarth, C.; Kommere, B.; Raeth, U.
CORPORATE SOURCE: (1) Dep. Intern. Med. IV, Univ. Heidelberg, Bergheimer Str. 58, D-69115 Heidelberg Germany
SOURCE: Hepato-Gastroenterology, (1995) Vol. 42, No. 6, pp. 1053-1061.
ISSN: 0172-6390.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Background/Aims: We report - as a retrospective observation - on eight patients with malignant carcinoid tumors. Materials and Methods: All patients were initially treated with alpha-interferon and received the longacting **somatostatin** analogue octreotide (SMS 201-995) after disease progression. Tumor growth was monitored by CT-scan or ultrasound. In addition, serum CgA and urinary 5-HIAA values were determined. Results: All patients responded with relief of symptoms within a few days after the start of octreotide therapy. A regression of the tumor size did not occur, however four patients showed no significant progress over a period of nine to more than eighteen months. The endocrine parameter chromogranin A - determined by immunoluminometric assay (ILMA)- was elevated in all eight patients regardless of symptoms and showed a close correlation with the

course of disease. The urinary 5-HIAA values were only elevated in seven patients. In addition, 123I-SMS 204-090 scintigraphy could be performed in six patients. Using this method most of the primary tumors and metastases could be detected. Conclusions: Only octreotide therapy showed a sufficient symptomatic control and has to be considered as progress in drug therapy for patients with malignant carcinoid tumors. In addition, chromogranin A is an interesting endocrine parameter for the followup of the secretory activity.

L16 ANSWER 7 OF 9 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1992:17403 BIOSIS
DOCUMENT NUMBER: BR42:5103
TITLE: **SOMATOSTATIN** RECEPTOR SCINTIGRAPHY A NEW SCINTIGRAPHIC TOOL IN THE MANAGEMENT OF INTESTINAL CARCINOIDS?.
AUTHOR(S): BIHL H; STERZ M; MACKE H; **EISENHUT M**; RAETH U
CORPORATE SOURCE: KLINIK NUKLEARMEDIZIN, KATHARINENHOSPITAL STUTTGART, W. GER.
SOURCE: EUROPEAN ASSOCIATION OF NUCLEAR MEDICINE CONGRESS, VIENNA, AUSTRIA, SEPTEMBER 1-5, 1991. EUR J NUCL MED, (1991) 18 (8), 577.
CODEN: EJNMD9. ISSN: 0340-6997.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L16 ANSWER 8 OF 9 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2001:468215 SCISEARCH
THE GENUINE ARTICLE: 434NG
TITLE: Ga-68-DOTA(o)-D phe(1)-tyr(3)-octreotide (DOTATOC): A new PET-ligand for imaging **somatostatin** receptors in meningiomas.
AUTHOR: Henze M (Reprint); Schuhmacher J; Hipp P; Kowalski J; Becker D W; Maecke H R; Debus J; **Haberkorn U**
CORPORATE SOURCE: Univ Heidelberg, Heidelberg, Germany; German Canc Res Ctr, D-6900 Heidelberg, Germany; Univ Basel Hosp, CH-4031 Basel, Switzerland
COUNTRY OF AUTHOR: Germany; Switzerland
SOURCE: JOURNAL OF NUCLEAR MEDICINE, (**MAY 2001**) Vol. 42, No. 5, Supp. [S], pp. 67P-67P. MA 249.
Publisher: SOC NUCLEAR MEDICINE INC, 1850 SAMUEL MORSE DR, RESTON, VA 20190-5316 USA.
ISSN: 0161-5505.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0

L16 ANSWER 9 OF 9 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 135:190390 CA
TITLE: Antisense oligonucleotide conjugates with **somatostatin** analogs for treatment of tumors associated with high leves of the **somatostatin** receptor
INVENTOR(S): **Eisenhut, Michael; Mier, Walter; Eritia, Ramon; Haberkorn, Uwe**
PATENT ASSIGNEE(S): Deutsches Krebsforschungszentrum Stiftung des Oeffentlichen Rechts, Germany
SOURCE: Ger. Offen., 16 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
DE 10006572	A1	20010823	DE 2000-10006572	20000214	<--
EP 1129725	A2	20010905	EP 2001-103466	20010214	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
US 2001029035	A1	20011011	US 2001-781980	20010214	<--

PRIORITY APPLN. INFO.: DE 2000-10006572 A 20000214

AB The present invention concerns an oligonucleotide conjugate between an antisense DNA to an essential gene and a **somatostatin** analog. The present invention concerns also this oligonucleotide conjugate contg. drug, preferably to the therapy of tumors, with which the **somatostatin** receptor (SSTR) is over-expressed. The antisense DNA, which may contain base analogs or a modified backbone, is preferably directed against the bcl-2 oncogene. Prepn. of octreotide analogs of **somatostatin** and their conjugation with antisense oligonucleotides is demonstrated.

=> d his

(FILE 'HOME' ENTERED AT 16:08:25 ON 31 JUL 2002)

FILE 'BIOSIS, MEDLINE, SCISEARCH, CA' ENTERED AT 16:10:03 ON 31 JUL 2002

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L1         86875 S ((SOMATOSTATIN ANALOG?) OR OCTREOTIDE OR SOMATOSTATIN OR OCTR
L2        226887 S OLIGONUCL? OR ANTISENSE
L3           771 S L1 AND L2
L4       1219308 S L3 AND CONJUGAT? OR LINK?
L5            56 S L3 AND (CONJUGAT? OR LINK?)
L6             2 S L1 (5N) (CONJUGAT? OR LINK?) (5N) (OLIGONUCL? OR ANTISENSE)
L7             2 DUP REM L6 (0 DUPLICATES REMOVED)
L8            38 DUP REM L5 (18 DUPLICATES REMOVED)
L9            27 S L8 AND PY=<2000
L10          337 S EISENHUT, M?/AU
L11           73 S MIER, W?/AU
L12            1 S ERITIA, R?/AU
L13          411 S HABERKORN, U?/AU
L14           21 S (L10 OR L11 OR L12 OR L13) AND SOMATOST?
L15           11 DUP REM L14 (10 DUPLICATES REMOVED)
L16            9 S L15 AND PY<=2001

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FIELD CODE - 'AND' OPERATOR ASSUMED 'L6  (2A) L16'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L7  (2A) L17'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L8  (2A) L18'
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FIELD CODE - 'AND' OPERATOR ASSUMED 'L9  (2A) L19'
L17       22711 L2 (2N) L4

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PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
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PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L7  (S) L17'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L8  (S) L18'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
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FIELD CODE - 'AND' OPERATOR ASSUMED 'L9  (S) L19'
L18      22711 L2 (S) L4

=> d his

     (FILE 'HOME' ENTERED AT 16:08:25 ON 31 JUL 2002)

     FILE 'BIOSIS, MEDLINE, SCISEARCH, CA' ENTERED AT 16:10:03 ON 31 JUL 2002
L1         86875 S ((SOMATOSTATIN ANALOG?) OR OCTREOTIDE OR SOMATOSTATIN OR OCTR
L2        226887 S OLIGONUCL? OR ANTISENSE
L3           771 S L1 AND L2
L4       1219308 S L3 AND CONJUGAT? OR LINK?
L5            56 S L3 AND (CONJUGAT? OR LINK?)
L6             2 S L1 (5N) (CONJUGAT? OR LINK?) (5N) (OLIGONUCL? OR ANTISENSE)
L7             2 DUP REM L6 (0 DUPLICATES REMOVED)
L8            38 DUP REM L5 (18 DUPLICATES REMOVED)
L9            27 S L8 AND PY=<2000
L10          337 S EISENHUT, M?/AU
L11           73 S MIER, W?/AU
L12            1 S ERITIA, R?/AU
L13          411 S HABERKORN, U?/AU
L14           21 S (L10 OR L11 OR L12 OR L13) AND SOMATOST?
L15           11 DUP REM L14 (10 DUPLICATES REMOVED)
L16            9 S L15 AND PY<=2001
L17        22711 S L2 (2N) L4
L18        22711 S L2 (S) L4

=> s l2 s (conjuga? or link?)
MISSING OPERATOR L2 S
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l2 (s) (conjuga? or link?)
L19      18576 L2 (S) (CONJUGA? OR LINK?)

=> s l2 (2n) (conjuga? or link?)
L20       5408 L2 (2N) (CONJUGA? OR LINK?)

=> s l20 and somatost?
L21          12 L20 AND SOMATOST?

=> dup rem l21
PROCESSING COMPLETED FOR L21
L22            7 DUP REM L21 (5 DUPLICATES REMOVED)

=> d l22 1-7 ibib abs

L22  ANSWER 1 OF 7  CA  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         136:359644  CA
TITLE:                    Compositions for enhanced delivery of bioactive
                          molecules
INVENTOR(S):              Lewis, Danny; Schmidt, Paul; Hinds, Kenneth
PATENT ASSIGNEE(S):       PR Pharmaceuticals, Inc., USA
SOURCE:                   PCT Int. Appl., 24 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.   DATE
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WO 2002036169 A2 20020510 WO 2001-US45154 20011031
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2000-244499P P 20001031

AB Formulations for controlled, prolonged release of bioactive mols. such as therapeutic proteins, peptides and oligonucleotides have been developed. These formulations are based on solid microparticles or nanoparticles formed of the combination of biodegradable, synthetic polymers such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and copolymers. Bioactive mols. are coupled to hydrophilic polymers such as polyethylene glycol or polypropylene glycol and formulated to provide controlled release. The bioactive mols. are more stable, less immunogenic and have improved release rate profiles with lower burst levels and increased drug loading relative to the same bioactive mols. lacking coupled hydrophilic polymers. The controlled release formulations can be administered by injection, by inhalation, nasally, or orally. Leu-enkephalin was covalently modified with polyethylene glycol. The peptide was converted to its PEG-modified form. PEG-leu-enkephalin was dissolved in a 1:9 DMSO:PBS mixt. to a final concn. of 50 mg/mL. PLGA was dissolved in methylene chloride to a final concn. of 200 mg/mL. The primary emulsion was created by homogenizing 200 .mu.L of the peptide soln. with 3 mL of the polymer soln. at 10,000 rpm for 3 min. After the solvent had evapd. and the microparticles had hardened, they were collected by filtration and dried in vacuo before anal. The particles were characterized for core loading encapsulation efficiency, and particle size. Covalent coupling of PEG 5000 to leu-enkephalin increased the drug loading attainable from 0.07 to 0.36 % for the double emulsion technique and from 0.3 to 3.95 % for the monophase method.

L22 ANSWER 2 OF 7 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 135:190390 CA
TITLE: **Antisense oligonucleotide conjugates** with **somatostatin** analogs for treatment of tumors associated with high leves of the **somatostatin** receptor
INVENTOR(S): Eisenhut, Michael; Mier, Walter; Eritia, Ramon; Haberkorn, Uwe
PATENT ASSIGNEE(S): Deutsches Krebsforschungszentrum Stiftung des Oeffentlichen Rechts, Germany
SOURCE: Ger. Offen., 16 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10006572	A1	20010823	DE 2000-10006572	20000214
EP 1129725	A2	20010905	EP 2001-103466	20010214
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2001029035	A1	20011011	US 2001-781980	20010214

PRIORITY APPLN. INFO.: DE 2000-10006572 A 20000214

AB The present invention concerns an **oligonucleotide**

conjugate between an **antisense** DNA to an essential gene and a **somatostatin** analog. The present invention concerns also this **oligonucleotide conjugate** contg. drug, preferably to the therapy of tumors, with which the **somatostatin** receptor (SSTR) is over-expressed. The antisense DNA, which may contain base analogs or a modified backbone, is preferably directed against the bcl-2 oncogene. Prepn. of octreotide analogs of **somatostatin** and their **conjugation** with **antisense** **oligonucleotides** is demonstrated.

L22 ANSWER 3 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:300098 BIOSIS
DOCUMENT NUMBER: PREV200100300098
TITLE: Tumor-targeting peptide-**oligonucleotide** **conjugates.**
AUTHOR(S): Mier, W. (1); Eritja, R. (1); Mohammed, A. (1); Haberkorn, U. (1); Eisenhut, M. (1)
CORPORATE SOURCE: (1) Nuclear Medicine, Universitaetsklinikum Heidelberg, Heidelberg Germany
SOURCE: Journal of Cancer Research and Clinical Oncology, (2001) Vol. 127, No. Supplement 1, pp. S44. print.
Meeting Info.: Eleventh Congress of the Division of Experimental Cancer Research of the German Cancer Society Heidelberg, Germany April 04-06, 2001 German Cancer Society . ISSN: 0171-5216.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L22 ANSWER 4 OF 7 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 134:25369 CA
TITLE: Oligonucleotides for inhibition of gastric acid production and/or secretion
INVENTOR(S): Tachas, George
PATENT ASSIGNEE(S): Australia
SOURCE: PCT Int. Appl., 164 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000071164	A1	20001130	WO 2000-AU498	20000524
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1185303	A1	20020313	EP 2000-926576	20000524
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: AU 1999-510 A 19990524
WO 2000-AU498 W 20000524

AB Methods are provided for the treatment or prevention of gastric acid disturbances and for reducing the breakdown of acid sensitive agents in the gastrointestinal tract. Also provided is a method for transfecting

parietal cells in vivo. Synthetic oligonucleotides are provided which may be used in these methods.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 5 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
ACCESSION NUMBER: 2001:65051 BIOSIS
DOCUMENT NUMBER: PREV200100065051
TITLE: Preparation and evaluation of tumor-targeting peptide-**oligonucleotide conjugates**.
AUTHOR(S): Mier, Walter (1); Eritja, Ramon; Mohammed, Ashour; Haberkorn, Uwe; Eisenhut, Michael
CORPORATE SOURCE: (1) Department of Nuclear Medicine, Universitaetsklinikum Heidelberg, INF 400, 69120, Heidelberg: walter_mier@med.uni-heidelberg.de Germany
SOURCE: Bioconjugate Chemistry, (November December, 2000) Vol. 11, No. 6, pp. 855-860. print.
ISSN: 1043-1802.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Enormous progress has been made in the development of antisense oligodeoxynucleotides (ODNs) as therapeutic agents inhibiting gene expression. Unfortunately, the therapeutical application of ODNs is still held back because of the low cellular uptake and the lack of specific transport into particular cells. In this paper, we report a drug-targeting system using **somatostatin** receptors (SSTRs) which are overexpressed in various tumors. Phosphorothioate ODNs were covalently linked to Tyr3-octreotate, an analogue of **somatostatin**. The peptide was assembled by solid-phase synthesis, oxidized to form the cyclic disulfide, and subsequently derivatized with a N-terminal maleimido functionality. 5'-Thiol derivatized phosphorothioate-ODNs directed against the protooncogene bcl-2 were conjugated to this maleimido-modified peptide. Binding studies revealed that the conjugates retain specific binding with nanomolar affinities to SSTRs (IC50-values between 1.83 and 2.52 nM). Furthermore, melting studies with complementary DNA revealed that the terminal conjugation of the ODNs did not significantly affect their hybridization affinity.

L22 ANSWER 6 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
ACCESSION NUMBER: 1996:335931 BIOSIS
DOCUMENT NUMBER: PREV199699058287
TITLE: Estimation of the number of **somatostatin** neurons in the striatum: An in situ hybridization study using the optical fractionator method.
AUTHOR(S): West, Mark J. (1); Ostergaard, Karen; Andreassen, Ole A.; Finsen, Bente
CORPORATE SOURCE: (1) Dep. neurobiol., Inst. Anat., Univ. Aarhus, 8000 Aarhus Denmark
SOURCE: Journal of Comparative Neurology, (1996) Vol. 370, No. 1, pp. 11-22.
ISSN: 0021-9967.
DOCUMENT TYPE: Article
LANGUAGE: English

AB **Somatostatin**-containing neurons of the striatum constitute fewer than 5% of the total neuronal population. Their involvement in the feedforward inhibition of the spiny projection neurons, the modulation of other interneurons, and the regulation of regional blood flow indicates that this small population of neurons plays an important role in the processing of information in the striatum. As a first step in developing a quantitative structural framework within which a more rigorous analysis can be made of the functional circuitry of the striatum, we used modern

unbiased stereological techniques to make estimates of the total number of neurons expressing mRNA for **somatostatin** in the striatum of rats. The strategy developed involved the application of the optical fractionator technique to relatively thick tissue sections that were hybridized in situ with a relatively short **oligonucleotide** probe **conjugated** to a nonradioactive reporter molecule. The approach is generally applicable to other subpopulations of in situ hybridized cells in other parts of the brain and can provide a link between molecular neurobiology and stereology. The mean total number of neurons on one side of the striatum was estimated to be 21,300. An analysis of the sampling scheme indicated that counting no more than 200 neurons in a systematic sample of not more than 15 sections per individual results in an estimate with a precision that is more than sufficient for comparative and experimental studies. The issues that must be considered when analyzing in situ hybridized tissue with modern stereological methods, the interpretive caveats inherent in the resulting data, and the unique perspectives provided by data like that presented here for striatal **somatostatin** neurons are discussed.

L22 ANSWER 7 OF 7 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 96:29414 CA
TITLE: A polypeptide product and a plasmidic expression vehicle for it, a method of creating an expression plasmid, a method of cleaving double stranded DNA, and specific plasmids
INVENTOR(S): Kleid, Dennis G.; Yansura, Daniel G.; Heyneker, Herbert L.; Miozzari, Giuseppe F.
PATENT ASSIGNEE(S): Genentech, Inc., USA
SOURCE: Eur. Pat. Appl., 51 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 36776	A2	19810930	EP 1981-301227	19810323
EP 36776	A3	19821027		
EP 36776	B1	19880511		
R: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
ZA 8101368	A	19820428	ZA 1981-1368	19810302
FI 8100876	A	19810925	FI 1981-876	19810320
DK 8101299	A	19810925	DK 1981-1299	19810323
DK 173085	B1	19991227		
NO 8100986	A	19810925	NO 1981-986	19810323
BR 8101712	A	19810929	BR 1981-1712	19810323
AU 8168636	A1	19811001	AU 1981-68636	19810323
AU 542640	B2	19850228		
GB 2073203	A1	19811014	GB 1981-8986	19810323
GB 2073203	B2	19840229		
FR 2480781	A1	19811023	FR 1981-5732	19810323
FR 2480781	B1	19851018		
JP 56145221	A2	19811111	JP 1981-40529	19810323
JP 07024582	B4	19950322		
DE 3111405	A1	19820325	DE 1981-3111405	19810323
DE 3111405	C2	19900621		
ES 500617	A1	19820916	ES 1981-500617	19810323
DD 159435	C	19830309	DD 1981-228534	19810323
EP 86548	A2	19830824	EP 1983-200301	19810323
EP 86548	A3	19831130		
EP 86548	B1	19870520		

R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

HU 27459	O	19831028	HU 1981-732	19810323
HU 195534	B	19880530		
DD 203746	A5	19831102	DD 1981-243408	19810323
DD 204494	A5	19831130	DD 1981-243409	19810323
EP 154133	A2	19850911	EP 1985-100548	19810323
EP 154133	A3	19860528		
EP 154133	B1	19900516		

R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

CS 238612	B2	19851216	CS 1981-2106	19810323
CS 238645	B2	19851216	CS 1983-6230	19810323
CS 238646	B2	19851216	CS 1983-6231	19810323
IL 62460	A1	19860131	IL 1981-62460	19810323
IL 71885	A1	19860131	IL 1981-71885	19810323
AT 27306	E	19870615	AT 1983-200301	19810323
AT 34183	E	19880515	AT 1981-301227	19810323
AT 52802	E	19900615	AT 1985-100548	19810323
DE 3153606	C2	19910425	DE 1981-3153606	19810323
PL 147727	B1	19890731	PL 1981-252630	19810324
PL 162227	B1	19930930	PL 1981-230296	19810324
ES 509935	A1	19830316	ES 1982-509935	19820226
ES 509936	A1	19830401	ES 1982-509936	19820226
US 4663283	A	19870505	US 1983-543682	19831020
AU 580959	B2	19890209	AU 1984-29964	19840627
AU 8429964	A1	19841018		
AU 585832	B2	19890629	AU 1984-29963	19840627
AU 8429963	A1	19841018		
NO 8403718	A	19810925	NO 1984-3718	19840918
NO 161572	B	19890522		
NO 161572	C	19890830		
NO 8403719	A	19810925	NO 1984-3719	19840918
NO 165644	B	19901203		
NO 165644	C	19910313		
FR 2555199	A1	19850524	FR 1984-19450	19841219
FR 2555199	B1	19870904		
FI 8503488	A	19850912	FI 1985-3488	19850912
FI 8503489	A	19850912	FI 1985-3489	19850912
FI 72344	B	19870130		
FI 72344	C	19870511		
JP 05211885	A2	19930824	JP 1992-274165	19921013
JP 06073469	B4	19940921		
JP 05268962	A2	19931019	JP 1992-274172	19921013
JP 07034747	B4	19950419		
US 5888808	A	19990330	US 1993-55960	19930429
US 6333174	B1	20011225	US 1995-482321	19950606

PRIORITY APPLN. INFO.:

US 1980-133296	A	19800324
FI 1981-876	A	19810320
EP 1981-301227	A	19810323
EP 1985-100548	A	19810323
IL 1981-62460	A	19810323
US 1981-307473	A3	19811001
US 1984-685521	B1	19841224
US 1987-76253	B1	19870721
US 1989-345047	B1	19890427
US 1991-655215	B1	19910212
US 1991-773740	B1	19911009

AB Plasmids are prepd. to contain (1) a linear double-stranded DNA fragment contg. a replicon and a gene which expresses a selectable characteristic when placed under the control of a bacterial promoter, (2) a 2nd DNA fragment contg. a gene of a desired product, and (3) a 3rd DNA fragment contg. a bacterial promoter, with all 3 DNA fragments in the same reading frame. The activity of the gene in (2) is regulated by growing bacteria

contg. the plasmids in media contg. appropriate concns. of an effector of the bacterial promoter (3). Thus, plasmid pBRHtrp was constructed by digesting the known plasmid pGM1, which contains an Escherichia coli tryptophan (trp) operon, with restriction endonuclease PvuII and joining **oligonucleotide linkers** to the PvuII fragment contg. the trp promoter-operator region. The **oligonucleotide linkers** contained recognition sites for restriction endonuclease EcoRI, which permitted insertion of the trp fragment into the EcoRI cleavage site of plasmid pBRH1 and ligation with phage T4 DNA ligase to give plasmid pBRHtrp. Plasmid pSOM7.DELTA.2, with a **somatostatin** gene under control of the trp promoter, was constructed by recovering the promoter-contg. DNA from pBRHtrp with endonuclease EcoRI and inserting the DNA into the EcoRI site of plasmid pSom11 (Itakura, K., et al., 1977). Escherichia coli Transformed with pSOM7.DELTA.2 formed a protein consisting of **somatostatin** fused to a short segment of the protein encoded by gene trpD. Formation of the fusion protein was repressed in media contg. high concns. of tryptophan. Immunol. reactive **somatostatin** was recovered from the fusion protein by CNBr cleavage.

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(FILE 'HOME' ENTERED AT 16:08:25 ON 31 JUL 2002)

FILE 'BIOSIS, MEDLINE, SCISEARCH, CA' ENTERED AT 16:10:03 ON 31 JUL 2002

L1	86875	S	((SOMATOSTATIN ANALOG?) OR OCTREOTIDE OR SOMATOSTATIN OR OCTR
L2	226887	S	OLIGONUCL? OR ANTISENSE
L3	771	S	L1 AND L2
L4	1219308	S	L3 AND CONJUGAT? OR LINK?
L5	56	S	L3 AND (CONJUGAT? OR LINK?)
L6	2	S	L1 (5N) (CONJUGAT? OR LINK?) (5N) (OLIGONUCL? OR ANTISENSE)
L7	2	DUP REM	L6 (0 DUPLICATES REMOVED)
L8	38	DUP REM	L5 (18 DUPLICATES REMOVED)
L9	27	S	L8 AND PY=<2000
L10	337	S	EISENHUT, M?/AU
L11	73	S	MIER, W?/AU
L12	1	S	ERITIA, R?/AU
L13	411	S	HABERKORN, U?/AU
L14	21	S	(L10 OR L11 OR L12 OR L13) AND SOMATOST?
L15	11	DUP REM	L14 (10 DUPLICATES REMOVED)
L16	9	S	L15 AND PY<=2001
L17	22711	S	L2 (2N) L4
L18	22711	S	L2 (S) L4
L19	18576	S	L2 (S) (CONJUGA? OR LINK?)
L20	5408	S	L2 (2N) (CONJUGA? OR LINK?)
L21	12	S	L20 AND SOMATOST?
L22	7	DUP REM	L21 (5 DUPLICATES REMOVED)